

EX B

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Genetics

Evidence in humans that there are susceptibility genes for autoimmunity comes from family studies and especially from studies of twins. Studies in IDDM, rheumatoid

arthritis, multiple sclerosis, and SLE have shown that approximately 15 to 30% of pairs of monozygotic twins show disease concordance, compared with <5% of dizygotic twins. The occurrence of different autoimmune diseases within the same family has suggested that certain susceptibility genes may predispose to a variety of autoimmune diseases. In addition to this evidence from humans, certain inbred mouse strains reproducibly develop specific spontaneous or experimentally induced autoimmune diseases, whereas others do not. These findings have led to an extensive search for genes that determine susceptibility to autoimmune disease.

The most consistent association for susceptibility to autoimmune disease has been with the major histocompatibility complex (MHC). Many human autoimmune diseases are associated with particular HLA alleles (Chap. 306). It has been suggested that the association of MHC genotype with autoimmune disease relates to differences in the ability of different allelic variations of MHC molecules to present autoantigenic peptides to autoreactive T cells. An alternative hypothesis involves the role of MHC alleles in shaping the T cell receptor repertoire during T cell ontogeny in the thymus. Additionally, specific MHC gene products themselves may be the source of peptides that can be recognized by T cells. Cross-reactivity between such MHC peptides and peptides derived from proteins produced by common microbes may trigger autoimmunity by molecular mimicry. However, MHC genotype alone does not determine the development of autoimmunity. Identical twins are far more likely to develop the same autoimmune disease than MHC-identical nontwin siblings, suggesting that genetic factors other than the MHC also affect disease susceptibility. Recent studies of the genetics of IDDM, SLE, and multiple sclerosis in humans and mice have shown that there are several independently segregating disease susceptibility loci in addition to the MHC.

There is evidence that several other genes are important in increasing susceptibility to autoimmune disease. In humans, inherited homozygous deficiency of the early proteins of the classic pathway of complement (C1, C4, or C2) is very strongly associated with the development of SLE. In mice and humans, abnormalities in the genes encoding proteins involved in the regulation of apoptosis, including Fas (CD95) and Fas ligand (CD95 ligand), are strongly associated with the development of autoimmunity. There is also evidence that inherited variation in the level of expression of certain cytokines, such as TNF- or IL-10, may also increase susceptibility to autoimmune disease.

A further important factor in disease susceptibility is the hormonal status of the patient. Many autoimmune diseases show a strong sex bias, which appears in most cases to relate to the hormonal status of women.